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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,616	04/13/2006	Enea Menegatti	2503-1211	1346

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EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,616	MENEGATTI ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to Applicant's Amendment and Remarks, filed 27 Mar 2008, in which claim 1 is amended change the scope and breadth of the claim, claim 7 is canceled, new claims 14 and 15 have been added, and claims 1-6 and 8-13 have been amended to improve language and better conform to U.S. practice and English grammar.

This application is the national stage entry of PCT/EP04/11236, filed 08 Oct 2004; and claims benefit of foreign priority document ITALY MI2003A002019, filed 17 Oct 2003.

Amended claims 1-6 and 8-15 are pending in the current application. New claims 14 and 15 have been added

Objections Withdrawn

Applicant's amendment, filed 27 Mar 2008, with respect to objections to the specification has been fully considered and is persuasive because it is now clear what text belongs in which section of the specification.

This objection has been withdrawn.

Applicant's amendment, filed 27 Mar 2008, with respect to objections to claim 12 has been fully considered and is persuasive because the method implicit in the disclosed active step is now clearly recited.

This objection has been withdrawn.

The following new or modified rejections are necessitated by Applicant's Amendment, filed 27 Mar 2008, in which claim 1 is amended change the scope and breadth of the claim, claim 7 is canceled, and new claims 14 and 15 have been added. Claims 2-6 and 8-15 depend from claim 1 and incorporate all limitations therein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 1-4, 8-9 and 11-13 and new claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friedman et al. (US Patent

5,744,155, issued 28 Apr 1998, of record) in view of Riley, Jr. (US Patent 5,055,303, issued 08 Oct 1991, of record).

Friedman et al. discloses an oil-in-water emulsion of submicron particles, or microemulsion, with a hydrophobic core of a fat or oil surrounded by a surfactant wherein the emulsion further comprises a drug and a mucoadhesive polymer hyaluronic acid. See abstract, lines 1, 4, 6-8 and 10-11. The drug envisioned for use in the invention includes the retinoid retinoic acid (column 6, line 22) and the surfactant is a phopholipid such as lecithin (column 3, line 60-62), meeting limitations of instant claims 1 and 2. Friedman et al. discloses the fat or wax of the hydrophobic phase is envisioned to be an aliphatic ester of hydrophobic acids, such as isopropyl myristate (a C14 fatty acid esterified with a C3 alchol), including C8-C22 fatty acids and C2-C6 short chain alcohols, obviating isopropyl palmitate disclosed in instant claim 4, a C16 fatty acid esterified with a C3 alcohol. Friedman et al. discloses the polymer hyaluronic acid may be present as free acids or salts (column 7, lines 16-17) with a preferred molecular weight of at least 50, 300, or 1,000 kDa (column 7, lines 54-56), and envisions mucoadhesive polymer treated with NaOH to give the sodium salt (column 10, lines 59-60), meeting the limitation disclosed in instant claim 8 "HA salts with organic inorganic bases with a molecular weight of 50-730 KDa or a high molecular weight of 750-1230 KDa" and the limitation disclosed in instant claim 1, wherein the hyaluronic acid is present as the sodium salt. The emulsion further contains pharmaceutical excipients such as EDTA, preservatives, and antioxidants (column 8, lines 21-22 and 24-25), meeting limitations of instant claims 9 and 11. Friedman et al. discloses the use of

tocopherol acetate, an α-tocopherol, in the hydrophobic phase (column 4, line 67), meeting limitations of instant claim 10. Friedman et al. discloses preparation of the emulsion followed by addition of an aqueous solution, or acceptable carrier, containing the hyaluronic acid and excipients such as EDTA, preservatives, and antioxidants, meeting limitations of instant claims 12 and 13. Friedman et al. cites Riley Jr., US Patent 5,055,303, as prior art disclosing bioadherent emulsions of the water-in-oil type (column 2, lines 35-40). Friedman discloses the bioadhesive polymer is present in the microparticle usually in a final concentration of 0.01% wt/vol. (column 7, lines 15-20) and an example in which the active agent, indomethacin, is present at 0.2% by wt. (column 11, lines 10-25), meeting the limitations of instant claim 14. For microparticles with an oil and aqueous mixture the density is no more than 1 g/1 ml, therefore 0.01% wt/vol is approximately 0.01% wt/wt. Friedman teaches the emulsions are applied to mucosal surfaces such as nasal, buccal, rectal and vaginal (column 2, lines 60-65) which are types of exterior, cutaneous, surfaces of a mammal and therefore describe percutaneous absorption, which is absorption through unbroken skin, and are therefore capable of performing the intended recited in instant claim 15.

Friedman et al. does not specifically disclose a water-in-oil type microemulsion. Friedman et al. does not specifically disclose the oil phase consisting of isopropyl palmitate.

Riley, Jr. teaches water-in-oil type emulsions, wherein the internal hydrophobic phase is greater than that of the external aqueous phase (column 1, lines 13-14) is prior

art, which discloses high internal phase ratio emulsions where the internal phase is greater than 70% (column 1, lines 16-17).

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the invention of Friedman et al. with a water-in-oil type microemulsion. Friedman et al. cites Riley Jr., US Patent 5,055,303, as prior art disclosing bioadherent emulsions of the water-in-oil type (column 2, lines 35-40). Friedman et al. discloses emulsions with bioadherent properties. One of ordinary skill in the art at the time of the invention would have been motivated to use the prior art technique of a bioadherent emulsion of the water-in-oil type to improve the emulsions with bioadherent properties of Friedman et al.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the invention of Friedman et al. wherein the oil phase consists of isopropyl palmitate. Friedman et al. discloses the fat or wax of the hydrophobic phase is envisioned to be an aliphatic ester of hydrophobic acids, such as isopropyl myristate (a C14 fatty acid esterified with a C3 alchol), including C8-C22 fatty acids and C2-C6 short chain alcohols. Isopropyl palmitate, disclosed in instant claim 4, is a C16 fatty acid esterified with a C3 alcohol. It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute a functional equivalent aliphatic ester of hydrophobic acids, isopropyl palmitate, for isopropyl myristate.

Response to Applicant's Remarks:

Applicant's Remarks, filed 27 Mar 2008, have been fully considered and not found persuasive.

Applicant describes various physical properties of the instant invention. However, it is apparent from what is disclosed that these characteristics are inherent to composition. For example, with regard to the viscosizing effect of hyaluronic acid Friedman teaches it is known that prolonged residence time and bioadhesion are caused by increased viscosity (column 1, lines 48-51 and column 2, lines 37-40).

Applicant remarks that one of ordinary skill in the art would not have a reasonable expectation of success in combining Friedman in view of Riley. However, as noted in Applicant's enclosure 2, "In contrast to ordinary emulsions, microemulsions form upon simple mixing of the components..." Therefore, based on this level of general knowledge, it is found that one of ordinary skill in the art would have a reasonable expectation of success in substituting one known element for another.

Applicant remarks that Friedman does not teach "microemulsions", but rather "emulsions" of microparticles. Applicant provides enclosures establishing the general state of knowledge to distinguish between the terms "microemulsions" and "emulsions". However, Cevc (Advanced Drug Delivery Reviews, 2004, 56, p675-711, cited in PTO-892) states that "The term microemulsion in pharmaceutical industry is predominately used to denote an emulsion... The name, misleadingly, suggests dimensions of the order of micrometers, but deviant term usage is common." (page 686, left column, second paragrph). Therefore one of skill in the pharmaceutical arts would look to the more specific definition within the pharmaceutical industry rather than the general knowledge and conclude that the term microemulsion and an emulsion are interchangable. Further, if the stability of the emulsion is a characteristic property of a

"microemulsion", Friedman specifically identifies unstable emulsions (Friedman, column 17, example 24 in lines 25-45) indicating that by contrast the other emulsions are stable. Regarding the visibly clear or isotropic nature of the emulsion taught by Friedman, the emuslion taught would be clear because the microparticles, with a weighted average diameter such as 97 +/- 24 nm (Friedman column 11, lines 20-25), are significantly smaller than the wavelengths of visible light, which ranges from 380-750 nm. See entry for microemulsions, paragraph 2 (Encyclopedia of Chemical Physics and Physical Chemistry, 2001, Institute of Physics Publishing, cited in PTO-892).

Applicant remarks that the instant invention provides a surprising and unexpected result of improved bioavailability and absorption rate. However, Friedman teaches that a bioadhesive polymer, such as sodium hyaluronate taught by Friedman, in a pharmaceutical emulsion leads to improved bioavailability and rate of drug absorption (Friedman, column 3, lines 25-40). Therefore this result is not unexpected over the teachings of the prior art.

Amended claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Friedman et al. (US Patent 5,744,155, issued 28 Apr 1998, of record) in view of Riley, Jr. (US Patent 5,055,303, issued 08 Oct 1991, of record) as applied to amended claims 1-4, 8-9 and 11-13 and new claims 14 and 15 above, and further in view of Smolinske (Handbook of Food, Drug, and Cosmetic Excipients, 1992, p 251, of record).

Friedman et al. in view of Riley, Jr. obviates the water-in-oil type microemulsion. The emulsion contains pharmaceutical excipients such as EDTA, preservatives, and

antioxidants (Friedman et al. column 8, lines 21-22 and 24-25). Friedman et al. discloses the use of tocopherol acetate, an α-tocopherol, in the hydrophobic phase (column 4, line 67), addressing part of the limitation of claim 10.

Friedman et al. in view of Riley, Jr. does not specifically disclose the emulsion containing parabens.

Smolinske teaches that parabens are a widely used drug and cosmetic preservatives (page 251, lines 8-9 and 11).

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the invention of Friedman et al. in view of Riley, Jr. containing parabens as preservatives. Smolinske teaches that parabens are widely used preservatives. It would have been obvious to one of ordinary skill in the art at the time of the invention to combine known prior art element to obtain predictable results. Therefore it would have been obvious to one of ordinary skill in the art at the time of the invention to practice the invention of Friedman et al. in view of Riley, Jr. wherein the disclosed preservatives are parabens as taught by Smolinske.

Response to Applicant's Remarks:

Applicant's Remarks, filed 27 Mar 2008, have been fully considered and not found persuasive.

Response to remarks with regard to Friedman and Friedman in view of Riley is as recited above.

Amended claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friedman et al. (US Patent 5,744,155, issued 28 Apr 1998, of record) in view of Riley, Jr. (US Patent 5,055,303, issued 08 Oct 1991, of record) as applied to amended claims 1-4, 8-9 and 11-13 and new claims 14 and 15 above, and further in view of Bonda (US Patent 6,551,605, issued 22 Apr 2003, of record).

Friedman et al. in view of Riley, Jr. obviates the water-in-oil type microemulsion containing the retinoid retinoic acid.

Friedman et al. in view of Riley, Jr. does not specifically disclose the use of the retinoid isoretinoin, tazarotene, or fenterinide.

Bonda teaches retinoids incorporated into an emulsion comprising a water-in-oil type emulsions, wherein the internal hydrophobic phase is greater than that of the external aqueous phase, incorporating retinoids, specifically isoretinoin, tazarotene, and fenretinide. See Bonda, column 6, lines 21-23 and 26, and exemplified in the composition of example 1, columns 5 and 6, lines 39-57.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the water-in-oil type microemulsion containing the retinoid retinoic acid of Friedman et al. in view of Riley, Jr. using the retinoids isoretinoin, tazarotene, and fenretinide taught by Bonda. Bonda teaches retinoids incorporated into a water-in-oil type emulsion. See Bonda example 1, columns 5 and 6, lines 39-57. It would have been simple substitution of functional equivalent retinoids known in the prior art to practice the invention of Friedman et al. in view of Riley, Jr. using the retinoid fenretinide in place of the retinoid retinoic acid to obtain predictable results. Therefore it would

have been obvious to one of ordinary skill in the art at the time of the invention to apply the teaching of Bonda to practice the water-in-oil type microemulsion of Friedman et al. in view of Riley, Jr. containing the retinoid fenretinide.

Response to Applicant's Remarks:

Applicant's Remarks, filed 27 Mar 2008, have been fully considered and not found persuasive.

Response to remarks with regard to Friedman and Friedman in view of Riley is as recited above.

Conclusion

No claim is found to be allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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